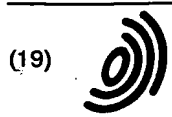


(10)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) **EP 0 895 777 A2**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
10.02.1999 Bulletin 1999/06

(51) Int. Cl.⁶: **A61K 7/48**, A61K 47/48,
A61K 7/16

(21) Application number: 98114153.4

(22) Date of filing: 29.07.1998

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: 05.08.1997 IT MI971882

(71) Applicant: Ausimont S.p.A.
20121 Milano (IT)

(72) Inventors:
• Bianchi, Ugo Plero
Verona (IT)
• Cavallotti, Claudio
Milano (IT)
• Antonini, Antonella
Parma (IT)

(74) Representative:
Sama, Daniele, Dr.
Sama Patents,
Via G.B. Morgagni, 2
20129 Milano (IT)

(54) **Compositions based on peroxyacids**

(57) Use of phthalimido-peroxycarboxylic acids in
the adduct form with cyclodextrins for preparing cos-
metic formulations.

EP 0 895 777 A2

Description

[0001] The present invention relates to bleaching and hygenizing compositions having high chemical stability which is maintained during the time also after prolonged storage (shelf stability) in complex formulations, for instance in cosmetic or pharmaceutical formulations.

[0002] More particularly the invention relates to compositions to be used for preparing tooth pastes or pharmaceutical compositions for the acne treatment.

[0003] The bleaching and hygenizing properties of the organic peroxyacids, specifically of the aliphatic peroxyphthalimdic acids, such as typically the epsilon-phthalimido peroxyhexanoic acid, known as PAP, are known, see for instance EP 325,289 and EP 325,288. The reactivity of the aliphatic peroxyphthalimdic acids makes their use in various applications interesting, but it is also a technical problem, from the point of view of the setting up of formulations having high stability during the time. Said organic peroxyacids indeed react very quickly wherefore it is not possible to prepare complex formulations stable during the time.

[0004] The shelf-stability of the formulation foreseen for the single application is therefore an important property. To this property it is necessary to combine other essential characteristics, consistent with the different applications, taking into account the industrial safety, logistic and the general and environmental toxicology of the various formulations. Said peroxyacids have particular technical and commercial importance due to their availability on the market and to the possibility to use them in granular preparations or in dispersions.

[0005] Among the organic peroxyacids and in particular the phthalimido-peroxyalkanoic acids most important applications, there are the typical ones of the cosmetic industry, in which the peroxyacid is introduced in systems formulated with many components and must be able to be effective under particularly mild conditions and to maintain its activity during the time also after storage.

[0006] As for the tooth pastes it is known the efficacy of the peroxyacetic acid, for the setting up of formulations with improved bleaching effect, see for instance the EP 545,594.

[0007] The efficacy of phthalimido-alkanoic and/or cationic peroxyacids for the preparation of tooth systems having a bleaching activity, is also known, see for instance the Patent Application WO 96/05802. In the case of the phthalimido-peroxyalkanoic acids, which have a remarkable chemical activity and bleaching and hygenizing activity, besides favourable toxicological characteristics, it is difficult to obtain unitary cosmetic formulations having polyfunctional characteristics. In this Patent Application, to prepare tooth pastes, a bicomponent system formed by two complementary but separate formulations, which are mixed the one to the other at the time of the use, is employed. This solution allows to maintain all the properties of the phthalimido-alkanoic peroxyacids but from the practical point of view it represents a limitation since it requires more complex equipments typical of the bicomponent systems.

[0008] The need was therefore felt to have available a formulation comprising the phthalimido-alkanoic peroxyacids as monocomponent composition.

[0009] It is known in the art to prepare adducts among peroxyacids and cyclodextrins. Specifically in EP 469,983, it is stated that the stability of the peroxydicarboxylic acids adducts is greater than that of the peroxydicarboxylic acid. In particular the heat-resistance, interpreted as lower tendency to the uncontrolled thermal decomposition, results greater for the adducts among peroxyacids and cyclodextrins, than that of the peroxyacids as such.

[0010] Specialistic technical literature is also known, see for instance D.M. Davies and M.E. Deary, "The interaction of alpha-cyclodextrin with aliphatic, aromatic and inorganic peracids, the corresponding parent acids and their respective anions" in J. Chem. Soc., Perkin Trans. 2, 1996, 2415-2421 and "Effect of alpha-cyclodextrin on the oxidation of aryl alkyl sulfides by peracids" 2423-2430; D.M. Davis et al. "Multiple pathways in the alpha-cyclodextrin catalysed reaction of iodide and substituted perbenzoic acids" in the same review 2, 1994 1531-1537. In these publications the specific chemical interaction between alpha-cyclodextrins and aliphatic, aromatic and inorganic peroxyacids, the reactivity and the nature of the chemical adducts obtained by interaction of the two components, are reported. From said publications it appears how the reactivity of the peroxyacids results marginally modified in the adducts with reference to the peroxyacids as such. The typical oxidation reactions of the iodide ion and of the R_a-S-R_a' group are reported, wherein R_a and R_a' are alkyls and/or aryls equal to or different from each other, in aqueous phase with the adducts and with the peroxyacids as such. These reactions occur in the adduct case in mild conditions, sometimes with even higher easiness with reference to the peroxyacids as such. This means that the reactivity of the peroxyacids present in the adducts is higher than that of the peroxyacids as such. See for instance the data reported for the peroxyacetic acid and for its adduct. The adducts therefore do not represent a chemically advantageous form to obtain formulations stable during the time.

[0011] The need was felt to have available complex formulations stable during the time of industrial interest in which the peroxyacid can be introduced without losing its reactivity characteristics.

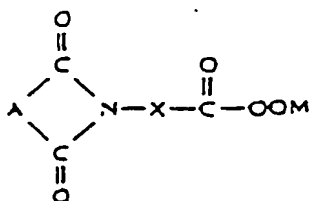
[0012] A process for preparing adducts among cyclodextrins, specifically betacyclodextrins, and organic peroxides selected from dialkyl- and diacyl-peroxides is also known, which find interest in the cosmetic product formulation. See for instance EP 441,690. It is a process based on the dispersion and the contact of the two components in water (80 parts) and ethanol (20 parts) mixtures, at temperatures in the range from 40° to 64°C.

[0013] It has been surprisingly and unexpectedly found that it is possible to prepare complex formulations comprising phthalimido-proxycarboxylic acids, in particular the epsilon-phthalimido-peroxyhexanoic acid, having high stability during the time and maintaining the typical proxyacid reactivity. This unexpected fact has allowed to prepare the above mentioned monocomponent formulations, with all the advantages resulting therefrom, for cosmetic, pharmaceutical and food applications.

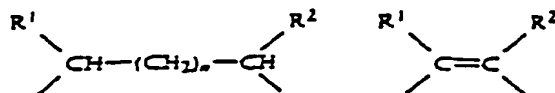
[0014] It is an object of the present invention the use of phthalimido-peroxycarboxylic acids, preferably of the epsilon-phthalimido-peroxyhexanoic acid, under the adduct form with cyclodextrins, preferably beta-cyclodextrins, for the preparation of cosmetic, pharmaceutical and food formulations.

[0015] The molar ratio between the invention peroxyacids and the cyclodextrins is in the range 1:1-1:2.

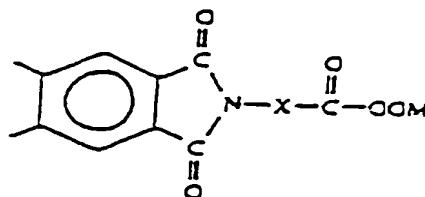
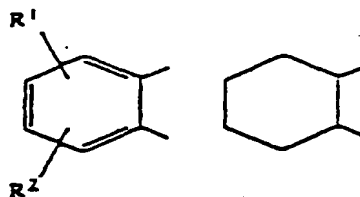
[0016] The imido-alkanperoxycarboxylic acids which can be treated according to the present invention use have the general formula:



wherein A indicates one group having the formula



or



n is an integer 0, 1 or 2,

R¹ is hydrogen, chlorine, bromine, C₁-C₂₀ alkyl,

C₂-C₂₀ alkenyl, aryl or alkylaryl,

R² is hydrogen, chlorine, bromine or one group having the formula -SO₃M, -CO₂M, -CO₃M, -OSO₃M,
 M indicates hydrogen, an alkaline metal or ammonium ion or the equivalent of an earth-alkaline metal ion,
 and X indicates C₁-C₁₉ alkylene or arylene;
 Y indicates a C₃-C₁₉ alkylene.

[0017] Among said imidoalkanpercarboxylic acids the epsilon-phthalimidoperoxyhexanoic acid is particularly preferred.

[0018] Among the cyclodextrins we can mention the alpha, beta, gamma or delta cyclodextrins, the modified alpha, beta, gamma or delta cyclodextrins with acyclic, alkylic, hydroxyalkylic groups, generally having from 1 to 10 carbon atoms, preferably from 2 to 6; the mixtures of said cyclodextrins and the mixtures of said cyclodextrins and of dextrins or linear oligosaccharides, beta-cyclodextrins are preferably used.

[0019] The peroxidic activity of such adducts, where there is the active oxygen typical of the free peroxyacid, is modified so to render possible to widen the technical applicability field of the peroxyacid itself to multicomponent systems typical of the cosmetic industry, wherein the free peroxyacid would not in practice be usable, due to chemical incompatibility reasons.

[0020] A further object of the invention is a process for preparing peroxyacid adducts and in particular the epsilon-phthalimido peroxyhexanoic acid, and the cyclodextrins and in particular the beta cyclodextrins, which foresees the direct contact of the two components dispersed in an aqueous phase at room temperature, under continuous stirring for a time ranging from 2 to 12 hours, preferably from 6 to 8 hours. After said time the aqueous dispersion is filtered and the solid is recovered and dried by the methods known in the art, preferably by treatment with dry air at moderate temperatures, preferably between 20° and 50°C. The above described process results of particular industrial interest since not high temperatures are used, preferably room temperature in not expensive and easily available equipments.

[0021] The cosmetic formulations comprise the well known typical components, for instance surfactants, among which we can mention octyloctonate, emollients such as glycerine, dispersants, oils and greases, perfumed essences, optionally fillers such as micronized silica, oxides such as for instance titanium oxide, etc. The adduct amount is generally in the range 1-20% and preferably 5-10%.

[0022] The pharmaceutical formulations comprise the known pharmaceutical excipients and an adduct amount generally in the range 1-30% by weight and preferably 10-20%.

[0023] The food formulations comprise the known food excipients and an adduct amount generally in the range 1-10% by weight and preferably 2-5%.

[0024] The application of the peroxyacid adducts and in particular of the epsilon-phthalimido peroxyhexanoic acid, and the cyclodextrins and in particular the beta cyclodextrins in simple or complex systems of cosmetic, pharmaceutical and food importance, is of remarkable interest for the operators skilled in the art.

[0025] Some examples are hereinafter reported for illustrative but not limitative purposes of the present invention.

EXAMPLE 1

[0026] 5,650 g of beta cyclodextrin are added at room temperature to an aqueous suspension of 1,856 g of epsilon-phthalimido-peroxyhexanoic acid (water content 17% by weight; title 93% by weight) in 16 l of demineralized water, maintained under continuous stirring.

[0027] After the addition, the stirring is continued for 12 hours, keeping the system at room temperature (about 20°C). The obtained pulp is then filtered, and the solid is recovered. After drying that in an air-circulation stove at 50°C for 96 hours, about 7 kg of adduct are thus obtained, with an active oxygen content of 1.1% by weight.

EXAMPLE 2

[0028] 297 g of beta-cyclodextrin and 46 g of wet epsilon-phthalimido-peroxyhexanoic acid (water content 17% by weight; title 95% by weight) are suspended in 800 ml of demineralized water at 30°C, by maintaining the system under stirring for 8 hours.

[0029] After filtering and drying (as in case 1) 320 g of adduct with an active oxygen content of 0.6% by weight are obtained.

[0030] The adduct thermal stability results in a peroxidic loss of 0.3%, after 3 days in an air-circulation stove at 50°C.

EXAMPLE 3

[0031] 38 g of dry epsilon-phthalimido-peroxyhexanoic acid (title 95% by weight) are added with 148 g of beta-cyclodextrin to 400 ml of demineralized water, maintained at room temperature and under stirring. Stirring is continued for 12 hours. After drying, 175 g of adduct with an active oxygen content of 1.1% by weight, are obtained.

EXAMPLE 4Tooth formulation

5 [0032] 10 g of adduct among beta-cyclodextrins and epsilon-phthalimido-peroxyhexanoic acid, obtained as in Example 1, are mixed to 200 g of a base tooth paste having a standard composition (in % by weight):

10	glycerine	35	%
	water	33	%
	hydrate silica	23	%
15	propylene glycol	3	%
	sodium laurylsulphate	1.25	%
20	tetrasodium pyrophosphate	1.2	%
	carboxymethylcellulose	1.2	%
25	perfumes	1	%
	titanium oxide	0.5	%
30	sweeteners	0.3	%
	trichlosan	0.3	%
35	sodium fluoride	0.25	%

40 [0033] The obtained paste is manufactured in a plasticized container and placed in an air-circulation stove, where it is maintained for 60 days at 37°C.

[0034] The noted peroxidic loss resulted of 5.7%.

[0035] For comparison, the peroxidic loss noted in the case of a corresponding product obtained by adding to 200 g of the standard tooth base 2.25 g of dry epsilon-phthalimido-peroxyhexanoic acid (titre 95% by weight) and operating in a similar way, resulted higher than 95% by weight.

EXAMPLE 5Cosmetic cream

50 [0036] 10 g of adduct among beta-cyclodextrins and epsilon-phthalimido-peroxyhexanoic acid, obtained as in Example 1, are mixed with 200 g of a base cream having a standard composition:

55

	cetearil glucoside	5.0	%
5	octyl octanoate	14.0	%
	C12/C15-octyl-octanoate	12.0	%
10	butyrospermum parkii	3.0	%
	dimeticone	2.0	%
	dimeticonol-dimeticone	1.5	%
15	oryzanol	0.5	%
	tocopherol/lecithin/ascorbyl palmitate/citric acid	0.08	%
20	water	59.32	%
	potassium cetyl phosphate	2.0	%
25	imidazolidinyl urea	0.25	%
	methylchloroisothiazolinone/methylisothiazolinone	0.15	%
30	disodium EDTA	0.20	%

35 [0037] The obtained cream is manufactured in a plasticized container and placed in an air-circulation stove, where it is maintained for 60 days at 37°C.

[0038] The noted peroxidic loss results lower than 10%, in comparison with a peroxidic loss higher than 98% noted for the corresponding system obtained by mixing to 200 g of the same base cream 2.5 g of dry epsilon-phthalimido-peroxyhexanoic acid (titre: 95%).

40 Claims

1. Use of phthalimido-peroxycarboxylic acids, in the form of adducts with cyclodextrins for preparing cosmetic, pharmaceutical and food formulations.
- 45 2. Use of phthalimido-peroxycarboxylic acids according to claim 1, wherein the acid is the epsilon-phthalimido-peroxyhexanoic acid.
3. Use of phthalimido-peroxycarboxylic acids according to claims 1 and 2, wherein the cyclodextrins are selected from alpha, beta, gamma or delta cyclodextrins; modified alpha, beta, gamma or delta cyclodextrins with acyclic, alkylic, hydroxyalkylic groups; mixtures of said cyclodextrins and mixtures of said cyclodextrins and dextrans or linear oligosaccharides, preferably beta-cyclodextrins.
- 50 4. Use of phthalimido-peroxycarboxylic acids according to claims 1 to 3, wherein the peroxyacid and the cyclodextrin molar ratio is in the range 1:1-1:2.
- 55 5. Cosmetic formulations comprising the adduct according to claims from 1 to 4.

6. Cosmetic formulations according to claim 5 for preparing tooth pastes.

7. Pharmaceutical formulations comprising the adduct according to claims from 1 to 4.

5 8. Pharmaceutical formulations according to claim 7 for the acne treatment.

9. Food formulations comprising the adduct according to claims from 1 to 4.

10. Phthalimido-peroxycarboxylic acids in the adducts form with cyclodextrins according to claims from 1 to 4.

10

11. Adducts according to claim 10 wherein the phthalimido-peroxycarboxylic acid is the epsilon-phthalimido-peroxy-hexanoic acid.

15

12. Process for preparing adducts according to claims from 1 to 4 which foresees the direct contact of the two components dispersed in an aqueous phase at room temperature, under continuous stirring for a time ranging from 2 to 12 hours, preferably from 6 to 8 hours; the filtering and the recovery of the solid, its drying, preferably by dry air treatment at moderate temperatures, preferably in the range 20°-50°C.

20

25

30

35

40

45

50

55